AGRICULTURAL BIOLOGY,
2018, V. 53, № 4, pp. 673-686
(SEL'SKOKHOZYAISTVENNAYA BIOLOGIYA)

ISSN 2412-0324 (English ed. Online)
ISSN 0131-6397 (Russian ed. Print)
ISSN 2313-4836 (Russian ed. Online)

UDC 636.018:573.22

doi: 10.15389/agrobiology.2018.4.673eng
doi: 10.15389/agrobiology.2018.4.673rus

INTERRELATION OF NERVOUS, IMMUNE, ENDOCRINE SYSTEMS AND NUTRITIONAL FACTORS IN THE REGULATION OF ANIMAL RESISTANCE AND PRODUCTIVITY

(review)

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The authors declare no conflict of interests
Received May 3, 2016

Abstract

Commercial livestock husbandry causes severe stress among animals resulting in up to 80 % emergence of secondary immunodeficiency. This review is an attempt to comprehensively analyze multiple interconnections between immune, neuroendocrine systems, together with nutrition, as essential factors for animal metabolism regulation, wellness, health, performance and productivity. Secretion of stress hormones and the degree of inhibition of the immune response depend on the type of animal's nervous system. Poor nutrition has a negative effect on the expression of immune response including humoral and cellular immunity synthesis of cytokine and plasma immunoreceptors (V.I. Fisinin et al., 2013; V.A. Galochkin et al., 2013; Y. Zhang et al., 2014; J.D. Ashwell et al., 2000; S. Cunningham-Rundles et al., 2005; V. Abhyankar et al., 2018; A. Haghikia et al., 2015; R.H. Oakley et al., 2013). Due to this relationship, immune, nervous and endocrine systems form virtual functionally integrated single super-system of immunobiological surveillance. Its purpose is to maintain body viability, efficiency and resistance to any physical, chemical, biological agents and psychosocial factors that can cause adverse effects or pathological conditions. The total body resistance reflects the combined effects of specific and nonspecific factors of innate and adaptive immune responses together with activity of a number of intracellular systems, including antioxidant-prooxidant system, monooxygenase, peroxisomal system (V.I. Lushchak, 2014; N. Sinha et al., 2015; V.A. Galochkin et al., 2015), which are together responsible not only for the neutralization of xenobiotics and endogenous toxins, but for the monitoring of homeostasis. Evolution of conceptual views on the immune system has developed into understanding of its function not only as a "shield and sword of the organism". In-deep look in immune function and mechanisms is unthinkable without examining immune system as a regulatory component of a single triad with the nervous and endocrine systems.

Keywords: productive animals, the immune system, nervous, endocrine regulation, nonspecific resistance, health, productivity

Animal productivity is closely connected with the functional activity of the immune system, which is a multicomponent and polyreactive system integrated with the other physiological body systems. If commercial animal husbandry results in severe stress, the proportion of livestock population with secondary immune deficiencies reaches 80%. The stresses and immune deficiencies precede numerous illnesses and directly induce pathological conditions of various degrees of severity reducing the volume and quality of animal husbandry products [1, 2].

The goal of this overview is to comprehensively analyze at interdisciplinary level the multiple interconnections essential for the formation of protective and regulatory functions of livestock in the context of livestock health and productivity.

In 2011, immunologists B.A. Beutler and J.A. Hoffmann were awarded a Nobel Prize in physiology and medicine for deciphering of revolutionary mecha-

nisms of immune system regulation. Their ideas were linked to the discovery and receptor protein trait of Toll-like receptors on cell surface activating the innate immune system, which had been previously believed to have been determined solely genetically [unlike adaptive immunity). The idea of a purely protective role of the immune system [protection against disease-producing and foreign factors) reigned until 1970-s, and still the function of maintaining genetic uniformity of cells in a living body [in the middle of the 20th century, Nobel Prize laureate F.M. Burnet introduced the term "the science of self") [3] is recognized as the most important function of the immune system. However, the understanding of this term in controlling homeostasis expands. Specifically, it has become almost axiomatic that a body forms a single and functionally undivided triad of regulatory systems: the nervous system, endocrine system and immune system [4-6]. The study of this triad requires interdisciplinary approach. Moreover, the task of identifying defensive mechanisms of a body cannot be solved without taking into account the following immunology phenomena: the general adaptation syndrome, the role of antioxidant and pro-oxidant systems, monooxygenase and peroxisomal systems, intracellular reparative processes, etc. The effects of multiple interconnections of the immune system with the nervous and endocrine systems and nutritive factors are rather numerous and cannot be ignored when developing new biologically active additives and feed additives.

The interaction between innate and acquired immunity. The innate immunity system is just the first line of defense against any foreign agents and begins at a molecular level. It is responsible for immediate nonspecific defense that does not include immunological memory about an antigen [7]. The adaptive immune system [also known as specific immune system) develops over days or weeks because it includes an antigen-specific response and creation of immunological memory due to which a subsequent encounter of the antigen is met with a quicker and stronger response. The initial mediators of adaptive immune response, the B-lymphocytes, produce antibodies neutralizing an antigen or mark the antigen for presentation to T-cells or subsequent destruction by macrophages [8]. As opposed to humoral immunity mediated by antibodies, the cell-mediated immunity is connected with T-cells, the lymphocytes produced by thymus gland. The subgroups of T-cells play different roles in the adaptive immune system: the cytotoxic T-killers attack and destroy alien cells, T-helpers amplify the immune response and help the function of the other lymphocytes, T-suppressors suppress and restrain the immune system [9].

The complement system, which includes about 20 protein factors activated in a cascade during immune response, irreversibly damages the structure and functions of an alien object. The phagocytosis dysfunction is often observed in case of lack of chemotactic polypeptides created during complement activation and ensuring phagocyte movement to the place of infection [10, 11]. The complement system modulates adaptive immune response and, as a component of both innate and adaptive immune system, may serve as an example of their interconnection.

The innate and acquired immunity function in unison via direct contact with the cells, and through the mediation of cytokine and chemokine communication molecules. i.e. small proteins contain cysteine that have chemotactic and attractant properties [12]. Consequently, an efficient immune system requires a coordinated effort of macrophages, neutrophiles, B- and T-lymphocytes with all other immune cell types. Furthermore, the immune response includes the growth of cell population of T-lymphocytes, reinforcing immunoglobulin synthesis with B-lymphocytes and acute-phase proteins with the formation of inflammatory mediators.

The cell-mediated response is required for lymphocyte clones to appear

and destroy objects with alien genetic information. Since diverse antigens can be found on the surface of alien cells, the immunoglobulins of different isotypes [A, M, G, E) are produced in activated plasmatic cells [13].

Stress and homeostasis. *Physiological stress*. In terms of physiological interpretation, stress can be defined as disturbance of internal equilibrium required for a living organism to respond in order to maintain psychophysiological integration. H.H.B. Selye, who outlined the triad necessary for all chromic stresses (involution of thymus-lymphatic system; hypertrophy of adrenal gland; stomach ulceration) [14], described maintaining stability of internal environment of a body as a generalized adaptation syndrome with a focus on adrenal cortex producing cortisol (corticosteroids). W. Cannon, the author of classic works on fight-or-flight response, who developed the definition of "stress" by introducing the term "homeostasis", focused on participation of sympathetic nervous system in stress response. At this time, the role of hypothalamic-pituitary-adrenal axis and sympathetic nervous system in the creation of a generalized response of a body to any stress [agent or event) is generally recognized.

Biochemical characteristics of stress. Oxidative metabolic stress. Intensive animal husbandry requires a widespread usage of preventive, therapeutic and stimulating means and technologies resulting in the emergence of additional chemical, biological and social factors causing stress to livestock population. During stress, a body generates an excessive amount of free radicals, which has a very negative impact on health of animals, their disease resistance and reduces the productivity and quality of products [15].

An in-depth analysis of state of all systems and formation of a generalized response to the incoming signals is possible only in the context of a supersystem of immunobiological control. It applies to the manifestations of nonspecific resistance. There exists a compelling opinion that immunobiological control should be understood as an interconnection of specific immune and non-specific biological factors and mechanisms of homeostasis directed against the agents and causes violating the structural and functional stability of the internal environment of a body and ensuring its preservation and recovery. These mechanisms are under genetic control and are regulated via direct correlations and response [16].

The activity of free-radical processes and lipid peroxidation required for normal operation of all intracellular components, regulation of lipid composition, fluidity and permeability of cytoplasmic membranes is biochemically homeostated [17] and is determined by tissue-specific balance of antioxidants and prooxidants. Oxidative stress occurs when the balance shifts in the direction of prooxidants [18] followed by disruption of defensive system functions and development of oxidative tissue damage. The free radicals are necessary for normal metabolism; however, their abundance has detrimental consequences [19]. The generality of free radical processes can be thought of as a unified mechanism of development of most (possibly, all) pathological process in any cell, tissue and organ regardless of pathology causes.

The almost strict dependence of suppression of free radical formation on activation of non-specific resistance systems on has always been observed [20]. The interconnection between loss of body resistance and increased activity of free radicals has also been observed. The metabolism controlled by the interaction among the nervous, immune and endocrine systems focuses specifically on their normalization during the initial stress phase [21]. Contemporary science has not yet managed to quantitatively assess the metabolic situation, the occurrence of which results in an uncontrolled overproduction of free radicals. A living organism has a multicomponent, in-depth antioxidant and antiradical system of defense [enzymatic and non-enzymatic) against oxidative stress [22], which is

a part of the non-specific resistance and immunobiological control.

Presently, the following catecholamines: adrenalin and noradrenaline are thought of as the main regulators of adaptive reactions [23]. They ensure fast, radical and relevant body response to stress due to their ability to initiate glycogenolysis and break down lipids, activate fatty acid oxidation, increase the concentration of glucose and unesterified fatty acids and triglycerols in blood, intensify the oxygen intake by tissues [24], change the luminal of vessels and bronchi, increase cardiac performance and performance of skeletal muscles [25], facilitate the agitation of the central nervous system. It is the catecholamines that are deemed to have the core function of establishing a link between the nervous, immune and endocrine systems via hypothalamus releasing factors, i.e. a large group of regulatory peptides common for these systems, and a cascade of hormones produced by the basal gland, as well as glands and cells synthesizing hormones in specific and non-specific organs [26].

The link between the hypothalamic-pituitary-adrenal axis and sympathetic part of the nervous system. Cerebral neurons in hypothalamus are the first to be stimulated in response to stress in order to synthesize and secrete corticotropin releasing hormone (CRH) and vasopressin (VP) [27]. The increased concentration of corticotropin releasing hormones and/or vasopressins in hypothalamic-pituitary portal blood initiates synthesis and secretion of neurohormones by the hypothalamus that activates the adrenal axis. The corticotropic cells of anterior pituitary gland stimulated by the corticotropin releasing hormones synthesize and secrete the adrenocorticotropic hormone (ACTH). In turn, the adrenocorticotropic hormone stimulates the production of glucocorticoids by the adrenal cortex. The glucocorticoids are responsible for negative hypothalamus and basal gland response via inhibiting the synthesis and/or secretion of corticotropin releasing factor, vasopressin и adrenocorticotropic hormone [28]. The implication is that vasopressin can stimulate the production of ACTH even at very low levels of CRH concentration. The glucocorticoid receptor can affect the hypothalamus-pituitary axis and can be inactivated by heat shock proteins hsp90, hsp70 and immunofilins, the low molecular weight proteins rich in cysteine that have the properties of cytokines. As a result of binding glucocorticoids with the receptors, the transcription of tissue-specific genes, which are related with the functioning of the immune system, is amplified or reduced, including synthesis of proinflammatory cytokines and anti-inflammatory cytokines, prostaglandins, cell adhesion molecules, etc. [29].

The sympathic nervous system is activated in response to numerous stress factors simultaneously with the hypothalamic-pituitary-adrenal axis or even earlier. Noradrenaline is secreted in case of stimulation of noradrenergic neurons in the brain and in postganglionic sympathetic neurons innervating the peripheral organs. Additionally, nerve impulse in the highest cortical centers from the brain transmits information for release of noradrenaline, serotonin and acetylcholine. The increased content of adrenaline in the brain acts as an alarm signal, which manifests itself in decreased neurovegetative activity, e.g. suppressed appetite and sleep disorders, and initiation of stress response via activation of the hypothalamic-pituitary-adrenal axis. Furthermore, noradrenaline secretion triggers the reactions of fear and aggression and boosts long-term memory of preserving hostile emotions reducing the functional activity of the immune system [30].

The reactions of the hypothalamic-pituitary-adrenal axis and sympathic nervous system are strictly and subtly interconnected. Both systems are activated in response to most stress factors and can synergistically produce response by helping each other. For instance, in the brain there exist reciprocal interconnections between noradrenaline and CRH, which activate each other. The release of

noradrenaline, serotonin and acetylcholine in the brain stimulated the secretion of CRH [31]. Similarly, noradrenaline induces the synthesis of ACTH and, correspondingly, of glucocorticoids. Likewise, CRH stimulates autonomic neurons in the brain stem for noradrenaline secretion [32]. The glucocorticoid receptors are also present in sympathetic neurons and enable glucocorticoids to regulate the synthesis, acceptance and noradrenaline content in brain tissue. The glucocorticoids can modulate the expression of β-adrenergic receptors via genomic and nongenomic mechanisms [33]. Together, catecholamine and glucocorticoids stimulate the cardiovascular system and catabolic effects, and inhibit numerous functions of the body, including the reproduction function and the immune system.

To summarize, the primary response to stresses of any aetiology is conducted by activating both the hypothalamic-pituitary-adrenal axis and the sympathic nervous system.

Stress, temperament and immune system. The hormonal panel analysis provides the most conclusive description of stress. The factors linked with the procedures associated with livestock breeding, e.g. weaning, castration, transportation, regrouping, tying, sudden change of ratios and quality of feeds, temperature conditions, negatively affect the immunity and productivity of animals. The behavioral response to challenges is differentiated and can be expressed as aggression, obedience, submission or adaptation. The response can be stronger or weaker depending on sensitivity of the animal [34]. The acute stress factors can multidirectionally affect the immune response, i.e. the effects can be immunosuppressive and immunomodulatory [35]. The chronic stresses usually result in suppression or dysfunction of innate and adaptive immune responses [36). Even under normal conditions the more excitable animals come close to stressed animals in terms of hormonal status, they have an increased basal concentration of glucocorticoids and catecholamines in blood, they are worse in terms of growth, their carcass quality is worse, and immune response in case of contact with pathogens is weaker. The increased concentration of glucocorticoids and catecholamines inhibits the immune system [37].

There are numerous works dedicated to the interconnections among the temperament, immune function and response of animals to stress factors, including tie-up and free stall housing. The cortisol concentration in young cattle stock is usually higher in case of free stall housing and goes down upon tie-up. Harsh treatment results in sharp decline of productivity and immune system of excitable (temperamental) animals and affects the calm animals to a lesser degree. The response to stresses of any aetiology is stimulated by different stress factors activating the hypothalamic-pituitary-adrenal axis and sympathetic nervous system [38].

The productivity and quality of the products are closely connected with behavioral response of animals and are reduced in case of negative emotions [39]. The stress hormone secretion, like immune response, depends on the temperament of animals. The calves with excitable (stress-non-resistant) temperament the basal concentration of cortisol and adrenaline is higher than that of calm animals [40]. Furthermore, in such animals the ACTH secretion in response to CRH is inhibited and in response to VP is boosted during depression. The nervous animals have a higher concentration of cortisol, and the calm animals the contents of neutrophils in blood positively correlates with cortisol concentration, which is not manifested in excitable animals [41]. The impact of temperament on production of stress hormones and the state of the immune system was identified in fattened male calves [41]. The easily excitable animals displayed a decline of the immune function along with reduction of the growth speed and carcass quality. In terms of lymphocyte proliferation and vaccine spe-

cific response (IgG products) the temperamental male calves were inferior to the calm ones. The excitable animals also showed a negative correlation between IgG and IgM concentration and lymphocyte proliferation (42). The cattle has higher population of B- and T-lymphocytes in blood, which identify antigens with membrane receptors and are responsible for immune response regulation, and the quantitative ratio of lymphocytes changes with age (43). The high concentration of catecholamines negatively affects the immune reactivity of cells treated with interleukines IL-1α and IL-1β. By affecting the secretion of cytokines with Th1 and Th2 T-helpers, the glucocorticoids and catecholamines can predominantly inhibit cell immunity controlled by Th1 cytokines, and not have the same active effect on Th2 cytokines controlled by humoral immunity [44].

To summarize, nervous animals display a higher degree of hypothalamic-pituitary-adrenal axis activation accompanied with suppressed immune response.

Nutritive factors and immune system. The nutrition, which is qualitatively and quantitatively deficient and can result in inadequate energy and nutrition substance ratio and deficit of a number of micronutrients (in some cases this can negatively affect the phagocytic function of innate immune system, synthesis of cytokines, antibodies and cell-mediated immunity), is the most frequent cause of immunodeficiencies and the risk factor of productive animals.

Macronutrients, food lipids. The disruptions of energy-protein feeds are the most frequent in animal husbandry, accompanied by the growth of vulnerability of livestock population to infections due to suppression of innate and adaptive immune systems [45]. Furthermore, the synthesis of certain cytokines and proteins of the complement systems is limited, the phagocytic function and cell-mediated immune reactions change [thymic atrophy occurs, the number of circulating T-cells declines along with the efficiency of immunological memory), the spleen and lymph node function is inhibited. The humoral immunity also suffers, the antibody affinity and response strength are reduced [16, 46].

Different food lipids are also connected to immune response modulation, first and foremost these are long-chain polyunsaturated fatty acids (LCPUSFA) ω-3 and ω-6, which are a part of the irreplaceable nutrient elements and should be received with food [47]. The eicosapentaenoic ($C_{20}H_{30}O_2$) and docosahexaenoic ($C_{21}H_{31}COOH$) ω-3 long-chain polyunsaturated fatty acids are involved in realization of the immune response and inflammatory response. They are included in the membranes of phospholipids of immune cells (including phagocytes and T-cells), induce the production of icosanoids, the 20-carbonic derivative of long-chain polyunsaturated fatty acids that play a key role in immune reactions, and other lipid mediators. In immune cell membranes the long-chain polyunsaturated fatty acids can metabolize enzymatically to icosanoids (prostaglandins, leukotrienes and thromboxanes) involved in the development of inflammatory response [16, 48].

The lipid mediators derived from the eicosapentaenoic and docosahexaenoic acids possess not only the anti-inflammatory properties, but are also capable of regulating the functions of T- and B-cells. Among icosanoids the derivatives of eicosapentaenoic acid are biologically less active than the derivatives of the arachidonic acid, therefore additions of eicosapentaenoic acid and other ω-3 long-chain polyunsaturated fatty acids are ineffective when treating inflammatory diseases. Presently, this area is actively studied because excessive consumption of ω-3 long-chain polyunsaturated fatty acids can suppress defensive mechanisms and increase vulnerability to infectious diseases [49]. The linoleic acid isomers [LA) with conjugated double bonds can modulate the immune function. The LA isomer cis-9, trans-11 is present in natural meat and milk of ruminant animals. It is also available as a food additive containing two LA isomer forms (cis-9, trans-11

and trans-10, cis-12). This additive increased the content of IgA and IgM in blood, while the number of proinflammatory cytokines declined and the number of anti-inflammatory cytokines increased [50].

Micronutrients: vitamins and minerals. The micronutrients play an essential role in the development and expression of immune response. Due to its immunosuppressive effect the deficit of specific micronutrients (vitamins, minerals) can have a negative impact on innate and adaptive immune system components increasing vulnerability to infectious and non-communicable diseases [51].

Vitamin A and its metabolites are involved in the reactions of the innate and adaptive immune systems. The skin and eye mucosa cells, as well as cells of the respiratory, gastrointestinal and genitourinary tract function as a barrier against infections (innate immune system). Vitamin A promotes the functioning of these mucosal cells and is necessary to maintain the activity of cells involved in the innate immune response (including natural killer cells, macrophages and neutrophils), and for the activity of T- and B-cells, the mediators of the adaptive immune system. Consequently, vitamin A is the essential factor of immune response. Vitamin A displays the key immune effects via the derivatives, specifically, via isomers of retinoic acid. The isomers of retinoic acid are steroid hormones, which are connected with retinoid receptors causing a cascade of molecular interactions initiating the expression of specific genes. The retinoic acid directly or indirectly regulates about 500 genes, some of which control cellular proliferation, which emphasizes the importance of vitamin A in the immune system [52].

The deficit of vitamin A results in immunodeficiency and increased risk of infectious diseases, especially at a young age. Vitamin A reduces the quantity and activity of killer cells. The subclinical deficiency of vitamin A increases the risk of infections, which, in turn, increase vitamin A deficiency in animals, including those caused by decreased feed intake, disorder of vitamin absorption and excretion, and reduced resorption. The impact of vitamin A on chemotaxis, phagocytosis and ability of immune cells to generate free radicals that destroy pathogens has been observed. By participating in the regulation of cytokine synthesis regulation vitamin A affects the development of inflammatory response of the innate immune system. The deficit of vitamin A affects humoral and cellular response of the adaptive immune system and has a particularly adverse effect on the growth and differentiation of B-cells that depend on retinol and its metabolites, and on manifestations of antibody response. The additions of vitamin A reduce the morbidity of diarrhea [53].

In terms of vitamin D, the function of the immune system modulator has been added to the impact on mineral homeostasis and bone metabolism. More than 200 genes are known, which are directly or indirectly regulated by dihydroxyvitamin D3. The receptor of vitamin D is expressed in immune cells of different types, including monocytes, macrophages, dendritic cells and activated T-cells. The macrophages also synthesize the hydroxyvitamin-D_3-1-hydroxylase enzyme, which locally converts vitamin D in its active form, which is involved both in the innate and adaptive immune responses. The antimicrobial peptides and cathelicidin are the key components of the innate immune system because they explicitly destroy pathogens, especially bacteria. The active form of vitamin D regulates cathelicidin synthesis and stimulates the other processes of the innate immune response, including proliferation of immune cells and biosynthesis of cytokines. By performing these functions vitamin D facilitates the increased efficiency of defense against infections. It suppresses the production of antibodies by B-cells and inhibits the proliferation of T-cells. Vitamin D can activate T-helpers and dendritic cells [54].

Vitamin C is a highly active natural antioxidant actively involved in innate and adaptive immune system response. Vitamin C functionally stimulates leucocytes, specifically neutrophils, lymphocytes and phagocytes (cell mobility, chemotaxis and phagocytosis). The neutrophils are the first line of cells activated by vitamin C [55]. At the same time it is believed to have an integrating role in the relations of immune cells. The neutrophils, mononuclear phagocytes and lymphocytes accumulate vitamin C in large quantities for protection of themselves and other cells against oxidative damage. The phagocytes produce a number of cytokines, including α-, β- and γ-interferons. The first two forms are thought of as classical and induced viruses, γ-interferon, being a typical cytokine, is synthesized by T- lymphocytes, natural killers and activated macrophages. Unlike α- and β-interferons, it actively stimulates the expression of components of the main complex of histocompatibility, antimicrobial and anti-tumor activity of macrophages and natural killers [56]. Furthermore, vitamin C is involved in regeneration of vitamin E from its oxidized form.

Vitamin E is an oil-soluble antioxidant; α-tocopherol form of vitamin E protects polyunsaturated fatty acid against peroxidation, which is the cause of damage of different cells of the immune system. The deficit of vitamin disrupts both the humoral and cell-mediated adaptive immune system, including the function of B- and T-cells. The additions of vitamin E above the recommended needs improve the immunity and reduce vulnerability to different infections, specifically at a young age [57). The functional activity of T-cells drops with age, which is confirmed by reduced proliferation and production by T-cells of cytokine IL-2 [58]. The experiments conducted on laboratory animals and clinical observations showed that vitamin E can compensate both age effects, improve the immune response on introduction of a vaccine against Hepatitis B and improve resilience against respiratory tract infections [59]. In other words, vitamin E can boost the immune system [60].

The deficiency of vitamin B_6 (pyridoxal) weakens the humoral and cell-mediated adaptive immune system. The specific effect of pyridoxal shortage manifests itself in suppression of proliferation, differentiation and maturation of lymphocytes, as well as biosynthesis of cytokines and antibodies. The adjusted content of pyridoxal in food ratios restores the affected immune functions [61].

The folic acid (Bc, B group vitamin) functions as a cofactor of enzymes transporting single-carbon fragments. The coenzymes containing folate act as acceptors and donators of single-carbon components in the endogenous synthesis reactions and RNA and DNA metabolism, as well as amino acids [62[. The deficiency of folate negatively affects the immune response, primarily the cell-mediated response. In case of folic acid deficiency the humoral arm of the immune system and antibody synthesis are suppressed [63].

Selenium is an essential element of the immune control system, it is a part of more than 30 enzymes (glutathione peroxidase, specifically) and vital biologically active compounds of animals. In case of selenium deficiency, animals, poultry and humans suffer numerous pathological changes similar to white-muscle disease, including T- and B- immunodeficiencies. Selenium affects the synthesis of IgG, IgM and IgA, lysozyme activity, β-lysines and general bactericidal activity, and activates the enzymatic antioxidant system [64]. By amplifying the activity of superoxide dismutase and glutathione peroxidase, selenium positively affects the non-specific resistance of the body, as well as cellular and humoral immune systems, which results in the growth of productivity and livability of animals and poultry [65]. Selenium additives stimulate immune response to foreign antigens, increase viral resistance, and expression of cytokines managing the immune response [66].

Zinc is a part of active centers of about 200 metalloenzymes and is through to be a critical element for the development and functioning of cells of the innate and adaptive immune system [67]. Zink does not accumulate in the body, it requires constant deliveries with feed. The Zn deficiency disrupts the complement system, cytotoxicity of natural killers, phagocytic activity of neutrophils and macrophages and ability of immune cells to generate free radicals that destroy pathogens. In case of strong Zn deficit, the immune system is suppressed and vulnerability to infectious agents increases [68].

Fe is involved in a number of immune functions, including differentiation and proliferation of T-lymphocytes, and in generation of reactive oxygen species neutralizing pathogens [69]. However, iron is also used by many infectious agents for reproduction and survival [70]. In case of acute inflammatory response, Fe concentration in blood serum decreases, and ferritin concentration increases. This is indicative of extraction of Fe, used by pathogens, as crucial response to infections. The increase of Fe concentration in blood, for instance, in case of hereditary haemochromatosis, can disrupt the immune system, biosynthesis of cytokines, complement activation and functions of T- and B-lymphocytes [71].

Copper plays an important role in the development and support of the immune system; however, the exact mechanisms of these interactions are still unclear. The copper deficit manifests itself as neutropenia, which can be the cause of significant increase of vulnerability to various infections [72]. At the same time it has been observed that chronic consumption of large copper doses negatively affects the immune system [73].

Probiotics [*immunobiotics*). More often than not these are lactobacilli and bifidobacteria, which are included in the ratios with fermentable products or as special additives. The probiotics are not digestible and access the colon, where they interact with receptors of intestinal epithelial and other cells associated with the immune system of the intestinal tract, including M- and dendritic cells [74]. The immune modulation effect is achieved only in case of constant intake of probiotics and change of intestinal flora. The probiotics have a positive effect on the innate and adaptive immune system [75], amplify epithelial intestinal barrier, including via inhibiting apoptosis and prolongation of life of intestinal epithelial cells, as well as stimulation of antibody production and proliferation of T-lymphocytes. The mechanism of impact of probiotics on the immune system of young livestock is rather complicated. As exemplified by *Lactobacillus jensenii* TL2937 strain, which in terms of its effects belongs to immunobiotics, this mechanism can broadly be described as follows [76]. A probiotic affects the signaling cascades of intestinal cells affecting the expression of cytokines and other proteins, and weakens the inflammatory response caused by the activation of a specific receptor of lymphocytes in lymphoid organs of intestinal walls. This process also involves the products of the major histocompatibility complex involved in antigen presentation to T- and B-lymphocytes. Consequently, the intestinal immunity of young livestock increases during the early postnatal period of ontogenesis. Since most of the cells of the immune system are localized in the intestinal mucosa and its mesogaster, the general immune status of animals is stimulated, which prevents the development of inflammatory intestinal disorders, diarrhea, allergies, gastrointestinal and other infections and improving health and growth of young livestock [77].

To summarize, the ability of the immune system to control the specifics of the internal environment of the body is implemented in conjunction with the nervous and endocrine systems. Together these systems, along with the antioxidant- pro-oxidant, monooxygenase and peroxisomal systems are combined in a suprasystem structure and ensure uniform immunobiological control of body re-

sistance. This structure maintains its resilience, control and metabolic regulation, as well as mobilization of non-specific resistance to the effect of any psychosocial, physical, chemical and biological agents and factors capable of causing adverse effect. The secretion of stress hormones and manifestation of immune response depend on the temperament of the animal because the hypothalamic-pituitary-adrenal axis and sympathetic nervous system are closely interconnected. The most frequent cause of immunodeficiency of productive animals is the deficiency of macronutrients and micronutrients. The interconnections between the immune, nervous and endocrine systems and nutritive factors are essential for the health and productivity of animals.

REFERENCES

1. Poryvaeva A.P., Krasnoperov A.S., Vereshchak N.A., Vaganova L.S. *Problemy veterinarnoi sanitarii, gigieny, ekologii*, 2017, 2: 83-87 (in Russ.).
2. Barashkin M.I. *Agrarnyi vestnik Urala*, 2015, 2: 113-119 (in Russ.).
3. Ribatti D. Peter Brian Medawar and the discovery of acquired immunological tolerance. *Immunol. Lett.*, 2015, 167(2): 63-66 (doi: 10.1016/j.imlet.2015.07.004).
4. Kalisch R., Müller M.B., Tüscher O. A conceptual framework for the neurobiological study of resilience. Behav. Brain Sci., 2015, 38(92): 1-79 (doi: 10.1017/S0140525X1400082X).
5. Hommers L., Raab A., Bohl A., Weber H., Scholz C.J., Erhardt A., Binder E., Arolt V., Gerlach A., Gloster A., Kalisch R., Kircher T., Lonsdorf T., Struhle A., Zwanzger P., Mattheisen M., Cichon S., Lesch K.P., Domschke K., Reif A., Lohse M.J., Deckert J. MicroRNA hsa-miR-4717-5p regulates RGS2 and may be a risk factor for anxiety-related traits. *Am. J. Med. Genet. Part B*, 2015, 168(4): 296-306. (doi: 10.1002/ajmg.b.32312).
6. Del Rey A., Besedovsky H.O. Immune-neuro-endocrine reflexes, circuits, and networks: physiologic and evolutionary implications. In: *Endocrine immunology*. W. Savino, F. Guaraldi (eds.). Front Horm Res. Basel, Karger, 2017, V. 48:1-18 (doi: 10.1159/000452902).
7. Panda S., Ding J.L. Natural antibodies bridge innate and adaptive immunity. *J. Immunol.*, 2015, 194(1): 13-20 (doi: 10.4049/jimmunol.1400844).
8. Cardamone C., Parente R., Feo G.D., Triggiani M. Mast cells as effector cells of innate immunity and regulators of adaptive immunity. *Immunol. Lett.*, 2016, 178: 10-14 (doi: 10.1016/j.imlet.2016.07.003).
9. Comrie W.A., Lenardo M.J. Molecular classification of primary immunodeficiencies of T lymphocytes. *Adv. Immunol.*, 2018, 138: 99-193 (doi: 10.1016/bs.ai.2018.02.003).
10. Dunkelberger J.R., Song W.C. Complement and its role in innate and adaptive immune responses. *Cell Res.*, 2010, 20(1): 34-50 (doi: 10.1038/cr.2009.139).
11. Surai P., Fisinin V.I. The modern anti-stress technologies in poultry: from antioxidants to vitagenes. *Sel'skokhozyaistvennaya Biologiya* [*Agricultural Biology*], 2012, 4: 3-13 (doi: 10.15389/agrobiology.2012.4.3eng).
12. Abhyankar V., Bland P., Fernandes G. The role of systems biologic approach in cell signaling and drug development responses — a mini review. *Med. Sci.*, 2018, 6(2): 1-9 (doi: 10.3390/medsci6020043).
13. Fisinin V.I., Surai P. *Ptitsevodstvo*, 2013, 5: 4-10 (in Russ.).
14. Goldstein D.S., McEwen B. Allostasis, homeostats, and the nature of stress. *Stress*, 2002, 5(1): 55-58 (doi: 10.1080/102538902900012345).
15. Galochkin V.A., Cherepanov G.G. *Problemy biologii produktivnykh zhivotnykh*, 2013, 1: 5-29 (in Russ.).
16. Cunningham-Rundles S., McNeeley D.F., Moon A. Mechanisms of nutrient modulation of the immune response. *J. Allergy Clin. Immunol.*, 2005, 115(6): 1119-1128 (doi: 10.1016/j.jaci.2005.04.036).
17. Galochkin V.A., Galochkina V.P., Ostrenko K.S. Development of theoretical bases and creation of antistress preparations of new generation for live-stock farming. *Sel'skokhozyaistvennaya Biologiya* [*Agricultural Biology*], 2009, 2: 43-55 (in Russ.).
18. Sinha N., Dabla P.K. Oxidative stress and antioxidants in hypertension — a current review. *Curr. Hypertens. Rev.*, 2015, 11(2): 132-142 (doi: 10.2174/1573402111666150529130922).
19. Lushchak V.I. Free radicals, reactive oxygen species, oxidative stress and its classification. *Chemico-Biological Interactions*, 2014, 224: 164-175 (doi: 10.1016/j.cbi.2014.10.016).
20. Jones D.P. Redefining oxidative stress. *Antioxidants & Redox Signaling*, 2006, 8: 1865-1879 (doi: 10.1089/ars.2006.8.1865).
21. Jones D.P. Radical-free biology of oxidative stress. *American Journal of Physiology—Cell Physiology*, 2008, 295(4): C849-C868 (doi: 10.1152/ajpcell.00283.2008).
22. Ostrenko K.S., Galochkina V.P., Galochkin V.A. Primenenie askorbata litiya dlya regulyatsii

lipidno-kholesterolovogo obmena i sistemy reduktsii glutationa u suporosnykh svinomatok. *Ukrainian Journal of Ecology*, 2018, 8(2): 59-66.
23. Belda X., Fuentes S., Daviu N., Nadal R., Armario A. Stress-induced sensitization: the hypothalamic-pituitary-adrenal axis and beyond. *Stress*, 2015, 18(3): 269-279 (doi: 10.3109/10253890.2015.1067678).
24. Zhao X.-J., Zhao Z., Yang D.-D., Cao L.-L., Zhang L., Ji J., Gu J., Huang J.-Y., Sun X.-L. Activation of ATP-sensitive potassium channel by iptakalim normalizes stress-induced HPA axis disorder and depressive behaviour by alleviating inflammation and oxidative stress in mouse hypothalamus. *Brain Res. Bull.*, 2017, 130: 146-155 (doi: 10.1016/j.brainresbull.2017.01.026).
25. Picard M., McManus M.J., Gray J.D., Nasca C., Moffat C., Kopinski P.K., Seifert E.L., McEwen B.S., Wallace D.C. Mitochondrial functions modulate neuroendocrine, metabolic, inflammatory, and transcriptional responses to acute psychological stress. *PNAS USA*, 2015, 112(48): 6614-6623 (doi: 10.1073/pnas.1515733112).
26. Lemos J.C., Wanat M.J., Smith J.S., Reyes B.A., Hollon N.G., Van Bockstaele E.J., Chavkin C., Phillips P.E. Severe stress switches CRF action in the nucleus accumbens from appetitive to aversive. *Nature*, 2012, 490: 402-406 (doi: 10.1038/nature11436).
27. Brindley R.L., Bauer M.B., Walker L.A., Quinlan M.A., Carneiro A.M.D., Sze J.Y., Blakely R.D., Currie K.P.M. Adrenal serotonin derives from accumulation by the antidepressant-sensitive serotonin transporter. *Pharmacol. Res.*, 2018, pii: S1043-6618(18)30429-8 (in press) (doi: 10.1016/j.phrs.2018.06.008).
28. Madalena K.M., Lerch J.K. The effect of glucocorticoid and glucocorticoid receptor interactions on brain, spinal cord, and glial cell plasticity. *Neural Plasticity*, 2017, 2017: Article ID 8640970 (doi: 10.1155/2017/8640970).
29. Ashwell J.D., Lu F.W., Vacchio M.S. Glucocorticoids in T cell development and function. *Annu. Rev. Immunol.*, 2000, 18(1): 309-345 (doi: 10.1146/annurev.immunol.18.1.309).
30. Lцwenberg M., Stahn C., Hommes D.W., Buttgereit F. Novel insights into mechanisms of glucocorticoid action and the development of new glucocorticoid receptor ligands. *Steroids*, 2008, 73(9-10): 1025-1029 (doi: 10.1016/j.steroids.2007.12.002).
31. Reeves J.W., Fisher A.J., Newman M.G., Granger D.A. Sympathetic and hypothalamic-pituitary-adrenal asymmetry in generalized anxiety disorder. *Psychophysiology*, 2016, 53(6): 951-977 (doi: 10.1111/psyp.12634).
32. Gil-Lozano M., Romanн-Pérez M., Outeirico-Iglesias V., Vigo E., González-Matías L.C., Brubaker P.L., Mallo F. Corticotropin-releasing hormone and the sympathoadrenal system are major mediators in the effects of peripherally administered exendin-4 on the hypothalamic-pituitary-adrenal axis of male rats. *Endocrinology*, 2014, 155(7): 2511-2523 (doi: 10.1210/en.2013-1718).
33. Oakley R.H., Cidlowski J.A. The biology of the glucocorticoid receptor: new signaling mechanisms in health and disease. *J. Allergy Clin. Immunol.*, 2013, 132(5): 1033-1044 (doi: 10.1016/j.jaci.2013.09.007).
34. Blalock J.E. The syntax of immune-neuroendocrine communication. *Immunology Today*, 1994, 15(11): 504-511 (doi: 10.1016/0167-5699(94)90205-4).
35. Edwards K.M., Morris N.B. Who's the boss: determining the control pathways of cardiovascular and cellular immune responses to acute stress. *Adv. Physiol. Educ.*, 2018, 42(2): 374-379 (doi: 10.1152/advan.00087.2017).
36. Zhang J.Y. Liu T.H., He Y., Pan H.Q., Zhang W.H., Yin X.P., Tian X.L., Li B.M., Wang X.D., Holmes A., Yuan T.F., Pan B.X. Chronic stress remodels synapses in an amygdala circuit-specific manner. *Biol. Psychiatry*, 2018, pii: S0006-3223(18)31633-0 (doi: 10.1016/j.biopsych.2018.06.019).
37. Curley K.O. Jr., Neuendorff D.A., Lewis A.W., Cleere J.J., Welsh T.H., Randel R.D. Functional characteristics of the bovine hypothalamic-pituitary-adrenal axis vary with temperament. *Hormones and Behavior*, 2008, 53(1): 20-27 (doi: 10.1016/j.yhbeh.2007.08.005).
38. Ramos R., Llabrés V., Monclús L., López-Béjar M., González-Solís J. Costs of breeding are rapidly buffered and do not affect migratory behavior in a long-lived bird species. *Ecology*, 2018, 0(0): Epub ahead of print (doi: 10.1002/ecy.2435).
39. Avitsur R., Padgett D.A., Sheridan J.F. Social interactions, stress, and immunity. *Neurologic Clinics*, 2006, 24(3): 483-491 (doi: 10.1016/j.ncl.2006.03.005).
40. Guzmán D.A., Lèche A., Contarde C.B., Nazar F.N., Marin R.H. Adrenocortical responses in Japanese quail classified by their permanence in proximity to either low or high density of conspecifics. *Poultry Sci.*, 2018, 0: pey269-pey269 (doi: 10.3382/ps/pey269).
41. Larauche M., Mulak A., Yuan P., Kanauchi O., Taché Y. Stress-induced visceral analgesia assessed non-invasively in rats is enhanced by prebiotic diet. *World J. Gastroenterol.*, 2012, 18(3): 225-236 (doi: 10.3748/wjg.v18.i3.225).
42. Savignac H.M., Kiely B., Dinan T.G., Cryan J.F. Bifidobacteria exert strain-specific effects on stress-related behavior and physiology in BALB/c mice. *Neurogastroenterol Motil.*, 2014, 26(11): 1615-1627 (doi: 10.1111/nmo.12427).
43. Savignac H.M., Tramullas M., Kiely B. Bifidobacteria modulate cognitive processes in an anxious mouse strain. *Behav. Brain Res.*, 2015, 287: 59-72 (doi: 10.1016/j.bbr.2015.02.044).

44. Zhang Y., Zhang Y., Gu W., He L., Sun B. Th1/Th2 cell's function in immune system. In: *T helper cell differentiation and their function. Advances in experimental medicine and biology*. B. Sun (ed.). Springer, Dordrecht, 2014, V. 841: 45-65 (doi: 10.1007/978-94-017-9487-9_3).
45. Jolly C.A., Fernandes G. Protein-energy malnutrition and infectious disease. In: *Nutrition and immunology: principles and practice*. M.E. Gershwin, J.B. German, C.L. Keen (eds.). Humana Press, Totowa, NJ, 2000: 195-202 (doi: 10.1007/978-1-59259-709-3_16).
46. Bourke C.D., Berkley J.A., Prendergast A.J._Immune dysfunction as a cause and consequence of malnutrition. *Trends Immunol.*, 2016, 37(6): 386-398 (doi: 10.1016/j.it.2016.04.003).
47. O'Shea M., Bassaganya-Riera J., Mohede I.C. Immunomodulatory properties of conjugated linoleic acid. *Am. J. Clin. Nutr.*, 2004, 79(6): 1199S-1206S (doi: 10.1093/ajcn/79.6.1199S).
48. Yaqoob P., Calder P.C. Fatty acids and immune function: new insights into mechanisms. *Brit. J. Nutr.*, 2007, 98(S1): S41-S45 (doi: 10.1017/S0007114507832995).
49. Miles E.A., Calder P.C. Fatty acids, lipid emulsions and the immune and inflammatory systems. In: *Intravenous lipid emulsions. World review of nutrition and dietetics*. P.C. Calder, D.L. Waitzberg, B. Koletzko (eds). Basel, Karger, 2015, V. 112: 17-30 (doi: 10.1159/000365426).
50. Haghikia A., Jörg S., Duscha A., Berg J., Manzel A., Waschbisch A., Hammer A., Lee D.H., May C., Wilck N., Balogh A., Ostermann A.I., Schebb N.H., Akkad D.A., Grohme D.A., Kleinewietfeld M., Kempa S., Thöne J., Demir S., Müller D.N., Gold R., Linker R.A. Dietary fatty acids directly impact central nervous system autoimmunity via the small intestine. *Immunity*, 2015, 43(4): 817-829 (doi: 10.1016/j.immuni.2015.09.007).
51. Richter F.C., Obba S., Simon A.K. Local exchange of metabolites shapes immunity. *Immunology*, 2018, 0(0): Epub ahead of print (doi: 10.1111/imm.12978).
52. Lo H.M., Wang S.W., Chen C.L., Wu P.H., Wu W.B. Effects of all-trans retinoic acid, retinol, and β-carotene on murine macrophage activity. *Food Funct.*, 2014, 5(1): 140-148 (doi: 10.1039/C3FO60309A).
53. Spinas E., Saggini A., Kritas S.K., Cerulli G., Caraffa A., Antinolfi P., Pantalone A., Frydas A., Tei M., Speziali A., Saggini R., Pandolfi F., Conti P. Can vitamin A mediate immunity and inflammation? *J. Biol. Reg. Homeos. Ag.*, 2015, 29(1): 1-6.
54. Sutton A.L., MacDonald P.N. Vitamin D: more than a "bone-a-fide" hormone. *Mol. Endocrinol.*, 2003, 17(5): 777-791 (doi: 10.1210/me.2002-0363).
55. Sorice A., Guerriero E., Capone F., Colonna G., Castello G., Costantini S. Ascorbic acid: its role in immune system and chronic inflammation diseases. *Mini-Reviews in Medicinal Chemistry*, 2014, 14(5): 444-452 (doi: 10.2174/1389557514666140428112602).
56. Berzina N., Markovs J., Dizhbite T., Apsite M., Vasilyeva S., Basova N., Smirnova G., Isajevs S. Oxidative stress and innate immunity status in chickens exposed to high dose of ascorbic acid. *Cell Biochem. Funct.*, 2013, 31(7): 551-559 (doi: 10.1002/cbf.2934).
57. Krueger L.A., Beitz D.C., Onda K., Osman M., O'Neil M.R., Lei S., Wattoo F.H., Stuart R.L., Tyler H.D., Nonnecke B. Effects of D-α-tocopherol and dietary energy on growth and health of preruminant dairy calves. *J. Dairy Sci.*, 2014, 97(6): 3715-3727 (doi: 10.3168/jds.2013-7315).
58. Sitrin J., Ring A., Garcia K.C., Benoist C., Mathis D. Regulatory T cells control NK cells in an insulitic lesion by depriving them of IL-2. *J. Exp. Med.*, 2013, 210(6): 1153-1165 (doi: 10.1084/jem.20122248).
59. El-Kannishy G., Arafa M., Abdelaal I., Elarman M., El-Mahdy R. Persistent oxidative stress in patients with chronic active hepatitis-C infection after antiviral therapy failure. *Saudi J. Gastroenterol.*, 2012, 18(6): 375-379 (doi: 10.4103/1319-3767.103429).
60. Reddy K.K., Ravinder T., Kanjilal S. Synthesis and evaluation of antioxidant and antifungal activities of novel ricinoleate-based lipoconjugates of phenolic acids. *Food Chem.*, 2012, 134(4): 2201-2207 (doi: 10.1016/j.foodchem.2012.04.046).
61. Cheng C.H., Chang S.J., Lee B.J., Lin K.L., Huang Y.C. Vitamin B_6 supplementation increases immune responses in critically ill patients. *Eur. J. Clin. Nutr.*, 2006, 60(10): 1207-1213 (doi: 10.1038/sj.ejcn.1602439).
62. Ströhle A., Bohn T. Folate and prevention of neural tube defects: new insights from a Bayesian model. *Int. J. Vitam. Nutr. Res.*, 2015, 85(3-4): 109-111 (doi: 10.1024/0300-9831/a000229).
63. Ströhle A., Wolters M., Hahn A. Safety of folic acid. *Med. Monatsschr. Pharm.*, 2015, 38(8): 297-306.
64. Galochkin V.A., Galochkina V.P. *Problemy biologii produktivnykh zhivotnykh*, 2008, 4: 3-20 (in Russ.).
65. Galochkin V.A., Cherepanov G.G. *Problemy biologii produktivnykh zhivotnykh*, 2013, 1: 5-29 (in Russ.).
66. Galochkin V.A., Agafonova A.V., Galochkina V.P., Cherepanov G.G. *Problemy biologii produktivnykh zhivotnykh*, 2015, 1: 5-24 (in Russ.).
67. Prasad A.S. Zinc in human health: effect of zinc on immune cells. *Mol. Med.*, 2008, 14(5-6): 353-357 (doi: 10.2119/2008-00033.Prasad).
68. Ibs K.H., Rink L. Zinc-altered immune function. *J. Nutr.*, 2003, 133(5): 1452S-1456S (doi: 10.1093/jn/133.5.1452S).
69. van Eijk L.T., Heemskerk S., van der Pluijm R.W., van Wijk S.M., Peters W.H., van der

Hoeven J.G., Kox M., Swinkels D.W., Pickkers P. The effect of iron loading and iron chelation on the innate immune response and subclinical organ injury during human endotoxemia: a randomized trial. *Haematologica*, 2014, 99(3): 579-587 (doi: 10.3324/haematol.2013.088047).
70. Khoshfetrat M.R., Mohammadi F., Mortazavi S., Rashidi A., Neyestani T., Kalantari N., Esmaillzadeh A. The effect of iron-vitamin C co-supplementation on biomarkers of oxidative stress in iron-deficient female youth. *Biol. Trace Elem. Res.*, 2013, 153(1-3): 171-177 (doi: 10.1007/s12011-013-9695-7).
71. Parveen N., Ahmad S., Shadab G.G. Iron induced genotoxicity: attenuation by vitamin C and its optimization. *Interdiscip. Toxicol.*, 2014, 7(3): 154-158 (doi: 10.2478/intox-2014-0021).
72. Beard J.L. Iron biology in immune function, muscle metabolism and neuronal functioning. *J. Nutr.*, 2001, 131(2): 568S-579S (doi: 10.1093/jn/131.2.568S).
73. Percival S.S. Copper and immunity. *Am. J. Clin. Nutr.*, 1998, 67(5): 1064S-1068S (doi: 10.1093/ajcn/67.5.1064S).
74. Bonham M., O'Connor J.M., Hannigan B.M., Strain J.J. The immune system as a physiological indicator of marginal copper status? *Br. J. Nutr.*, 2002, 87(5): 393-403 (doi: 10.1079/BJNBJN20020558).
75. de Vrese M., Schrezenmeir J. Probiotics, prebiotics, and synbiotics. In: *Food biotechnology. Advances in biochemical engineering/biotechnology*. V. 111. U. Stahl, U.E. Donalies, E. Nevoigt (eds.). Springer, Berlin, Heidelberg, 2008: 1-66 (doi: 10.1007/10_2008_097).
76. Ruemmele F.M., Bier D., Marteau P., Rechkemmer G., Bourdet-Sicard R., Walker W.A., Goulet O. Clinical evidence for immunomodulatory effects of probiotic bacteria. *J. Pediatr. Gastr. Nutr.*, 2009, 48(2): 126-141 (doi: 10.1097/MPG.0b013e31817d80ca).
77. Dowling D.J., Levy O. Ontogeny of early life immunity. *Trends Immunol.*, 2014, 35(7): 299-310 (doi: 10.1016/j.it.2014.04.007).